

Experience-dependent plasticity of white-matter microstructure extends into old age

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Abstract

Experience-dependent alterations in the human brain's white-matter microstructure occur in early adulthood, but it is unknown whether such plasticity extends throughout life. We used cognitive training and diffusion-tensor imaging (DTI) to investigate plasticity of the white-matter tracts that connect the left and right hemisphere of the frontal lobes. Over a period of about 180 days, twenty younger adults and 12 older adults trained for a total of 101 one-hour sessions on a set of three working memory, three episodic memory, and six perceptual speed tasks. Control groups were assessed at pre- and posttest. Training affected several DTI metrics and increased the volume of the anterior part of the corpus callosum. These alterations were of similar magnitude in younger and older adults. The findings indicate that experience-dependent plasticity of white-matter microstructure extends into old age and that disruptions of structural interhemispheric connectivity in old age, which are central to cognitive aging, are modifiable by experience and amenable to treatment.

Words: 158 (max 170)

Keywords: Plasticity; White-matter Microstructure; Cognitive Aging; Cognitive Training; Aging.

1. Introduction

The gray matter of the human brain shows structural plasticity in response to acquisition of new motor skills (Boyke et al., 2008; Draganski et al., 2004) and abstract knowledge (Draganski et al., 2006). Several findings also indicate that the brain's white matter displays experience-dependent changes in adulthood (Fields, 2008). For example, neural activity can induce myelination (Demerens et al., 1996; Stevens et al., 2002) and rhesus monkeys raised in enriched environments display larger corpus callosum size and improved cognitive performance (Mar Sánchez et al., 1998). In humans, amount of piano practicing in childhood and early adulthood correlates with white-matter microstructure as observed with diffusion-tensor imaging (DTI; Bengtsson et al., 2005) and young adults practicing juggling show microstructural changes in white matter (Scholz et al., 2009). Considering that impairments in white-matter integrity are a hallmark of cognitive aging (for reviews, see Madden et al., 2009a; Sullivan and Pfefferbaum, 2006), it is important to examine whether such plasticity extends into old age, and thus whether adult age-related differences in white-matter integrity are modifiable by experience and amenable to treatment.

We investigated the plasticity of white-matter microstructure in younger and older adulthood with a cognitive intervention. Twenty younger and 12 older adults participated in the cognitive intervention, which consisted of an average of 101 one-hour training sessions, each comprising practice on 12 different cognitive tasks, three related to working memory, three to episodic memory, and six to perceptual speed. Pretests and posttests conducted before and after training included DTI, which assess white-matter microstructure by quantifying free diffusion of water (mean diffusivity) as well as the directional rate (anisotropy) of water diffusion. Control groups took part in identical DTI measurements.

The cognitive tasks used in our intervention are known to activate the prefrontal cortices (Cabeza and Nyberg, 2000) and impose high attentional control demands that require interhemispheric communication (Banich, 1998; Mikels and Reuter-Lorenz, 2004). We therefore hypothesized that our intervention should affect the white-matter tracts that connect the prefrontal cortices. These tracts are located in the anterior part of the corpus callosum (i.e., genu; see Figure 1A). This region shows more pronounced age-related decline than more posterior regions of the corpus callosum (Burzynska et al., in press; Sullivan and Pfefferbaum, 2006). In addition, these age-related differences in structural connectivity can account for age differences in cognitive performance (Madden et al., 2009b) and functional brain activation (Persson et al., 2006; Sullivan and Pfefferbaum, 2006). Thus, from the perspective of aging research it is highly relevant to investigate the possibility of experience-dependent changes of the white-matter tracts connecting the prefrontal cortices. We therefore segmented (Niogi et al., 2007) and sub-segmented (Hofer and Frahm, 2006; Figure 1A) the corpus callosum on the pre- and posttest diffusion-tensor images from each participant. For each segment, we then obtained mean fractional anisotropy (FA), which is dependent on density and orientational coherence of white matter tracts, and mean diffusivity (MD), which taps barrier sparseness, and used these as primary dependent variables from the DTI data.

2. Materials and methods

2.1. Participants

Participants were recruited through newspaper advertisements, word-of-mouth recommendation, and flyers circulated in Berlin, Germany, for a longitudinal study on day-to-day variability of cognitive performance. This parent study involved 101 younger (aged 20-31 years) and 103 older adults (aged 65-80 years) completing an average of 101 cognitive practice sessions. Out of these participants, 30 younger and 27 older eligible volunteers were recruited for diffusion

tensor imaging (DTI) planned to take place before (pretest) and after (posttest) the cognitive intervention phase. Younger ($n = 11$) and older ($n = 13$) control groups were recruited to take part in imaging only. All participants were right-handed, had normal or corrected-to-normal vision, and reported no history of cardiovascular disease (except treated hypertension), diabetes, neurological or psychiatric conditions, or drug/alcohol abuse. They reported no use of anti-seizure or anti-depressant drugs. Older participants were screened for dementia using the mini-mental state examination (MMSE; Folstein et al., 1975) with a cut-off of 26.

Based on evaluations by a clinical neurologist, one younger and seven older intervention participants were excluded at pretest due to various brain abnormalities as observed on structural (T1) images. Due to technical failures or imaging artefacts (e.g., movement) at pretest, DTI data were lost for five younger and six older intervention participants. Four younger and two older intervention participants dropped out during the longitudinal phase of the study. In the control groups, one younger adult dropped out between pretest and posttest.

Thus, the effective sample for this article consisted of 20 younger (11 women; $M_{\text{age}} = 25.1$; $SD = 2.8$) and 12 older (7 women; $M_{\text{age}} = 68.9$; $SD = 2.7$) adults in intervention groups and 10 younger (4 women; $M_{\text{age}} = 25.6$; $SD = 2.6$) and 13 older (4 women; $M_{\text{age}} = 69.7$; $SD = 3.5$) adults in control groups. Intervention groups and control groups were statistically comparable on chronological age [$t(28) = 0.45$, NS, for young; $t(23) = 0.58$, NS, for old] and vocabulary (Lindenberger et al., 1993; cf. Lehrl et al., 1991) scores assessed at pretest ([$t(28) = 0.64$, NS, for young; $t(23) < 0.01$, NS, for old]).

Participants in the intervention groups were paid between 1450 and 1950 Euro, depending on the number of completed sessions and their pace of completing the longitudinal phase of the study. Participants in the control groups were paid 200 Euro. All participants gave written informed consent to participate. The ethical review board of the Otto-von-Guericke University of

Magdeburg approved the imaging sub-study and the review board of Max Planck for Human Development, Berlin, approved the behavioral parent study.

2.2. Training procedures

Intervention groups practiced three working memory, three episodic memory, and six perceptual speed tasks during on average 101 ($M_{\text{young}} = 102$, $SD_{\text{young}} = 3.3$; $M_{\text{old}} = 100$, $SD_{\text{old}} = 3.7$) sessions. Participants practiced individually in lab rooms containing up to six computerized testing stations. In addition, intervention groups completed behavioral pretests and posttests during ten sessions that consisted of 2-2.5hrs of cognitive test batteries and self-report questionnaires. A pretest brain-imaging session was conducted after the behavioral pretest and immediately before the longitudinal practice phase. The posttest imaging session was completed shortly after the completion of the behavioral posttest. The imaging sessions were separated by an average of 179 days ($M_{\text{young}} = 183$, $SD_{\text{young}} = 21.0$; $M_{\text{old}} = 173$, $SD_{\text{old}} = 25.2$). The control groups took part in imaging pretests and posttests only, which were separated by an average of 186 days ($M_{\text{young}} = 189$, $SD_{\text{young}} = 8.6$; $M_{\text{old}} = 184$, $SD_{\text{old}} = 15.0$).

The tasks practiced by the intervention groups were administered with several stimuli-presentation times at pretest, which allowed for estimation of time-accuracy functions. To maximize and even out the cognitive challenge of these tasks across individuals, while also maintaining motivation, the time-accuracy information was used for tailoring the difficulty of the subsequently practiced tasks by adjusting presentation time for each individual at the start of the intervention. Presentation times were kept constant over the intervention period. The practiced tasks are described in detail in the section below.

2.2.1. Spatial working memory: 3-Back

A sequence of 39 black dots appeared at varying locations in a 4 by 4 grid. Participants had to respond to each dot as to whether it was in the same position as the dot three steps earlier in the sequence or not. Four blocks were included in each daily session.

2.2.2. Numerical working memory: Memory updating

In each of four horizontally placed cells, four single digits (in the range of 0 to 9) was presented simultaneously for 4000ms. After an ISI of 500ms, eight updating operations were presented sequentially in a second row at varying horizontal position. The requested updating operations were additions and subtractions in the range of -8 to +8. Those updating operations had to be applied to the memorized digits from the corresponding cells above and the updated results had to be memorized. At the end of each trial, the four end results had to be entered in the four cells in the upper row. Eight blocks were included in each daily session.

2.2.3. Verbal working memory: Alpha span

Ten upper-case consonant letters were presented sequentially, together with a number below the letter. For each letter, participants had to decide as quickly as possible whether the number corresponds to the alphabetic position of the current letter within the set of letters presented up to this step. Five of the ten items were targets. Eight blocks were included in each daily session.

2.2.4. Figural-spatial episodic memory: Object-position memory

Sequences of 12 coloured photographs of real-world objects were displayed at different locations in a 6 by 6 grid. After presentation, objects appeared at the bottom of the screen and had to be moved in correct order to the correct locations by clicking on objects and locations with the computer mouse. Two blocks were included in each daily session.

2.2.5. Numerical episodic memory: Number-noun pairs

Lists of 12 two-digit numbers and nouns in plural case pairs were presented sequentially. After presentation, all numbers had to be entered prompted in random order by the nouns. Two blocks were included in each daily session.

2.2.6. Verbal episodic memory: Word lists

Lists of 36 nouns were presented sequentially. After presentation, the first three letters of each word had to be entered in correct order using the keyboard. Two blocks were included in each daily session.

2.2.7. Perceptual speed: Choice reaction tasks (CRT)

Three CRTs were based on the same stimulus layout, the seven lines of the number “8” as displayed on pocket calculators. Stimuli were masked with a stimulus that combined this “calculator 8” with extending lines in all 10 possible directions. Possible masking times were 1, 2, 4, or 8 screen cycles (12, 24, 47, or 94 ms). Depending on pretest performance, two out of these masking times (one fast and one slow condition) were chosen for each participant. Each CRT block consisted of 40 stimuli, 20 for the fast and 20 for the slow condition, with randomly chosen stimuli out of the two response categories. In the figural (symmetry) task, stimuli were either the upper or lower two lines to the left and right of the “calculator 8” (symmetric condition), or the two possible combinations of one upper and one lower line at the left and right (asymmetric condition). In the numerical (odd-even) task, stimuli were “3”, “5”, and “7”, for the odd and “2”, “4”, and “6” for the even condition. In the verbal (consonant-vowel) task, stimuli were “F”, “H”, and “P” for the consonant and “A”, “E”, and “U” for the vowel condition.

2.2.8. Perceptual speed: Comparison tasks

In the figural comparison task, two “fribbles”, coloured three-dimensional objects consisting of several connected parts, were shown to the left and right of the screen and participants had to decide as quickly as possible whether both objects were exactly the same or

different. If different, objects differed only by one part. Images of fribbles used in this task are courtesy of Michael J. Tarr, Brown University, <http://www.tarrlab.org/>. In the numerical comparison task, two strings of five numbers each appeared to the left and right of the screen and participants had to decide as quickly as possible whether both strings were exactly the same or different. If different, strings differed only by one number. Number strings were randomly assembled using digits 1 to 9. In the verbal comparison task, two strings of five letters each appeared to the left and right of the screen and participants had to decide as quickly as possible whether both strings were exactly the same or different. If different, strings differed only by one letter. Letters were lower case and randomly assembled from all consonants of the alphabet, precluding the possibility that they combined to real words. In each session, two blocks of 40 items were included for each comparison tasks, with equal numbers of same and different combinations.

2.3. Magnetic-resonance imaging (MRI) acquisition

At pretest and posttest, magnetic resonance images were acquired using a GE Signa LX 1.5-T system (General Electric, Milwaukee, WI) with actively shielded magnetic field gradients (maximum amplitude 40 mTm^{-1}). The MR protocol included a T1-weighted sagittal 3D scan (contrast-optimized spoiled gradient-echo sequence, 124 slices, slice thickness = 1.5 mm, FOV $250 \times 250 \text{ mm}^2$; 256×256 matrix; TE = 8 ms; TR = 24 ms; flip angle = 30°) and a single-shot diffusion-weighted spin-echo-refocused echoplanar imaging sequence (FOV $280 \times 280 \text{ mm}^2$; 128×128 matrix interpolated to 256×256 ; TE = 70 ms; TR = 10000 ms; 39 slices; slice thickness 3 mm; b-value 1000 s/mm^2). The data for diffusion tensor calculations were collected with 12 non-collinear gradient orientations, each additionally measured with the opposite diffusion gradient polarity. The orientations were chosen according to the DTI acquisition scheme proposed by Papadakis and colleagues (1999). The total of 24 diffusion-weighted measurements, each an

average of four measurements, were divided into four blocks, each preceded by a non-diffusion-weighted acquisition.

2.4. DTI analyses

The diffusion tensor images were eddy-current corrected (Bodammer et al., 2004) and then corrected for head motion based on the non-diffusion-weighted images (Woods et al., 1998). Diffusion tensors were calculated for each voxel and further decomposed into eigenvalues and eigenvectors. On the basis of the eigenvalues, mean diffusivity (MD) and fractional anisotropy (FA) maps and also maps displaying the axial and the radial diffusivity component were computed.

After exact sagittal alignment of the diffusion tensor data and coregistration of pretest and posttest images (with nearest-neighbor assignment) a semi-automated segmentation of the corpus callosum (CC) was performed using the algorithm described by Niogi and colleagues (2007) implemented in Matlab (Mathworks Inc., Natick, MA). This approach classifies voxels as potentially being part of the CC dependent on the voxels' principal diffusion direction in combination with the voxel-inherent FA. This segmentation step was controlled by visual inspection to avoid that voxels were erroneously classified as belonging to the CC. For this purpose, we modified Niogi and colleagues' algorithm slightly. In our implementation, groups of connected CC candidate voxels form clusters, from which the operator selects those that constitute the CC. Only voxels selected for both the pretest and the posttest dataset (the intersection) were used for further analysis. The voxels obtained from nine consecutive midsagittal slices were then automatically subdivided into five partitions by applying the scheme presented by Hofer and Frahm (2006; Figure 1A). Mean pretest and posttest values of MD, FA, and also axial and radial diffusivity were extracted from all CC partitions for each participant and time point.

2.5. Segmentation of T1 MRI data

To assess the midsagittal area of the CC, we first manually aligned the T1-weighted 3D dataset exactly along the interhemispheric fissure and then manually segmented CC on the midsagittal slice. For all data sets the operator was blinded to the time of assessment and group status. The voxels obtained from the midsagittal slice were then automatically subdivided into the five partitions by applying the scheme used for the DTI analyses (Hofer and Frahm, 2006; Figure 1A).

2.6. Statistical analyses

The inclusion of control groups enables dissociation of true intervention-related changes from confounding changes, such as maturation, aging-related decline, and time-of-year effects. With a control-group design, the critical intervention effect is revealed by an interaction between time of assessment (pretest vs. posttest) and experimental group (intervention vs. control); that is, changes between pretest and posttest for intervention groups that are significantly different from those for control groups. Similarly, age-related differences in intervention effects are revealed by an interaction between age group, time of assessment, and experimental group. To address these effects, we performed a series of univariate 2 (Time; Pretest vs. Posttest) X 2 (Experimental group; Intervention vs. Control) X 2 (Age group; Young vs. Old) mixed Analyses of Variance (ANOVAs) separately for mean MD and FA of each of the five corpus callosum segments. These analyses were followed up with paired t-tests to probe the significance of the changes for each group separately. The threshold for significance was .05.

Because the cognitive data was only available for the intervention groups, we analyzed changes in performance for these groups with paired t-tests for each age group and task separately. Finally, we correlated changes in performance on the twelve cognitive tasks (i.e., difference scores; posttest-pretest) with changes in FA and MD in the intervention groups. These

correlations were computed separately for the two age groups, as well as with the two age groups collapsed. For these correlation analyses, the threshold for significance (.05) was corrected for multiple comparisons.

3. Results

Results from ANOVAs applied to the primary DTI data (Figure 1, Table 1 and 2) revealed intervention-related change in the form of an interaction between experimental group (intervention vs. control) and time (pretest vs. posttest) for MD (Figure 1B) in segment 1 (genu) of the corpus callosum, $F(1,51) = 4.40, p = .041$. MD decreased in both the younger, $t(19) = 2.57, p = .019$, and the older intervention group, $t(11) = 2.39, p = .036$. The control groups showed no significant changes, both $ts < 0.21$, not significant (NS). FA (Figure 1C) displayed a similar pattern of intervention-related change in segment 1, $F(1,51) = 6.08, p = .017$. The older intervention group increased significantly in FA, $t(11) = 3.12, p = .010$, but the increase for the younger intervention group did not reach significance, $t(19) = 1.64$, NS. The control groups showed no significant changes, $ts < 1.22$, NS. Note that the age by experimental group by time interaction were neither significant for MD nor for FA, both $F_s(1,51) < 1.84$, NS, indicating that the intervention-related effect did not differ significantly between age groups. No other segment displayed significant intervention-related change, $F_s(1,51) < 1.75$, NS.

Task performance increased over time for all tasks for both younger, all $ts(19) > 2.70, ps < .014$, and older adults, all $ts(11) > 2.30, ps < .042$. No significant correlation between changes in performance on the twelve cognitive tasks and changes in FA and MD was observed.

Finally, we performed complementary analyses of radial and axial diffusivity in segment 1. Here, the ANOVAs revealed a significant intervention-related decrease in radial (Figure 2A), $F(1,51) = 6.60, p = .013$, but not in axial (Figure 2B), $F(1,51) < 0.03$, NS, diffusivity. In addition,

we observed significant intervention-related volume increase for the midsagittal area of segment 1 (Figure 3) on structural high-resolution images, $F(1,51) = 22.88$, $p < .001$.

4. Discussion

This study shows that white-matter microstructure, as indexed by FA and MD obtained from the anterior part of the corpus callosum, is modifiable by experience in both younger and older adulthood. These results add validity to evidence of experience-dependent plasticity of white matter in early adulthood (e.g., Fields, 2008; Scholz et al., 2009) and reveal that such plasticity extends into old age, thereby clearly demonstrating that experience can change white-matter microstructure well beyond periods of the lifespan during which maturational myelination occurs. The cognitive tasks that we used to induce experience-related white-matter changes are all known to involve the prefrontal cortices (Cabeza and Nyberg, 2000) and demand attentional control that requires interhemispheric communication (Banich, 1998; Mikels and Reuter-Lorenz, 2004). Thus it is likely that our intervention, which was massive in terms of the range of practiced tasks, intensiveness, and extensiveness, induced these changes. In addition, factors such as the increased social stimulation due to the extensive training procedure may have contributed to the observed effects. Regardless of the relative contribution of these factors, our findings lead to the novel conclusion that experience-dependent plasticity of white-matter microstructure is also present in later adulthood.

Though great care should be taken when linking observed changes in DTI metrics to potential histological changes (e.g., Wheeler-Kingshott & Cercignani, 2009), our complementary analyses of radial (i.e., perpendicular) and axial (i.e., parallel) diffusivity of the most anterior segment of corpus callosum reveal an intriguing pattern of changes in radial, but not in axial, diffusivity – a pattern that has been linked to myelination (Alexander et al., 2007; Song et al., 2005). In addition, we observed significant intervention-related volume increase for this segment.

This finding argues against dehydration as a cause of the observed diffusivity changes. The possibility that experience may induce an increase in myelination is well compatible with the observation that myelination is not static across adulthood. Rather, there is complex and ongoing dynamics of demyelination and myelination across adulthood (Bartzokis, 2009; Wozniak and Lim, 2006), possibly pointing to a persistent potential for experience-dependent plasticity. In this vein we note that the analyses did not detect any significant age-related differences in plasticity of white-matter microstructure, which contrasts with reports of age-related decline in plasticity of gray matter (e.g., Boyke et al., 2008) and cognitive performance (e.g., Kliegl et al., 1989).

Our findings inform research on several disorders (e.g., schizophrenia and late-onset Alzheimer's disease) in which disrupted connectivity is a major cause for dysfunction (Bartzokis, 2009; Feng, 2008; Fields, 2008) and are particularly applicable to aging-related cognitive decline. White-matter microstructure in the genu is linked to cognitive decline in aging (Madden et al., 2009b) and to increases of activation in the prefrontal cortices during cognitive tasks (Persson et al., 2006). These age-related functional differences might partially be accounted for by reductions in the efficiency of inter-hemispheric communication (O'Sullivan et al., 2001; Sullivan and Pfefferbaum, 2006) and disruption of synchronous operation of brain networks (Andrews-Hanna et al., 2007), stemming from age-related white-matter degradation (Sullivan and Pfefferbaum, 2006). Though we did not detect any significant associations between altered white-matter microstructure and improvements in cognitive performance in this study, which is not surprising considering the limited sample size for analyzing between-person differences, our findings open new opportunities for future studies to address how improved white-matter microstructure might enhance such neural processes. That is, the discovery of experience-dependent plasticity of white-matter microstructure in later human adulthood adds promise to attempts to attenuate cognitive impairments in aging.

Acknowledgements

Funded by the Max Planck for Human Development, the Innovation Fund of the Max Planck Society, the Sofja Kovalevskaja Award (to ML) administered by the Alexander von Humboldt Foundation and donated by the German Federal Ministry for Education and Research (BMBF), Deutsche Forschungsgemeinschaft, and the BMBF. We thank Colin Bauer, Annette Brose, Christian Chicherio, and all research assistants.

Disclosure Statement

No conflicts of interest.

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Figure Captions

Figure 1. (A) Midsagittal slice of a MD dataset showing corpus callosum sub-segmented (Hofer and Frahm, 2006) into regions likely connecting the prefrontal (1; genu), premotor and supplementary motor (2), motor (3), sensory (4), and temporal, parietal, and occipital (5; splenium) cortices. **(B)** Mean change (Δ ; \pm SE) from pretest to posttest in mean diffusivity and **(C)** fractional anisotropy in segment 1 (genu) of the corpus callosum as a function of age and experimental group.

Figure 2. Mean change (Δ ; \pm SE) from pretest to posttest in **(A)** radial diffusivity and **(B)** axial diffusivity in segment 1 (genu) of the corpus callosum as a function of age and experimental group.

Figure 3. Mean area (number of voxels; \pm SE) of segment 1 (genu) of the corpus callosum on the midsagittal slice as a function of age, experimental group, and time of assessment.

Figure 1

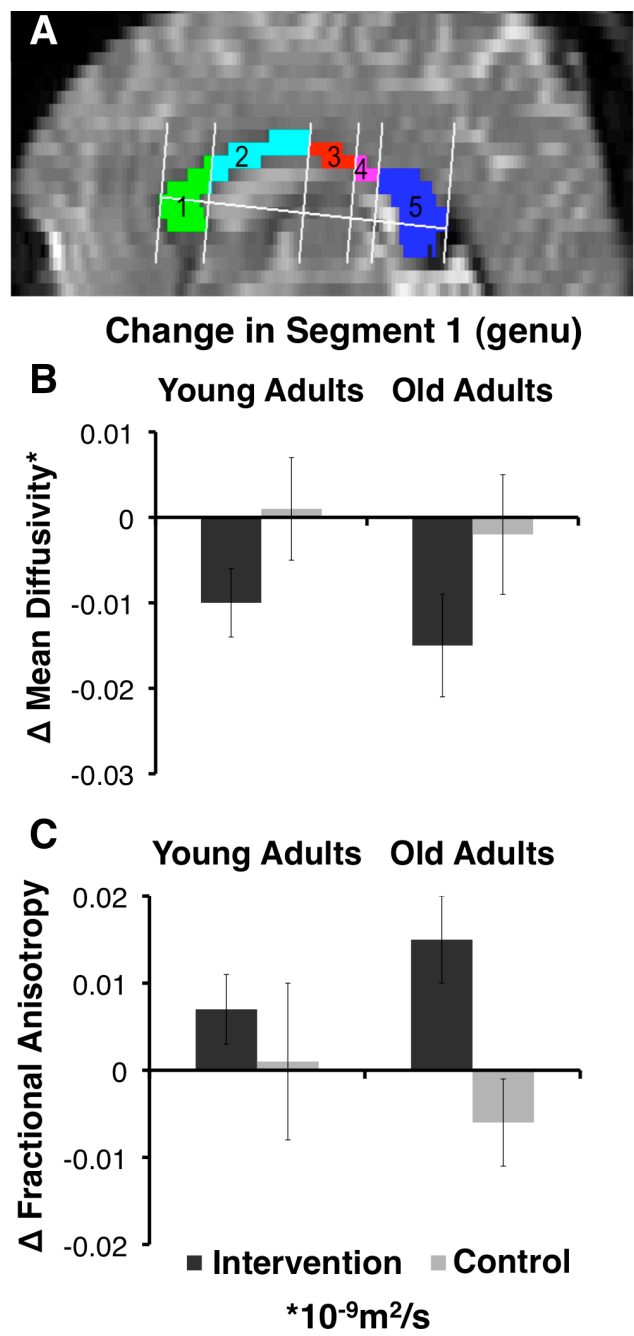


Figure 2

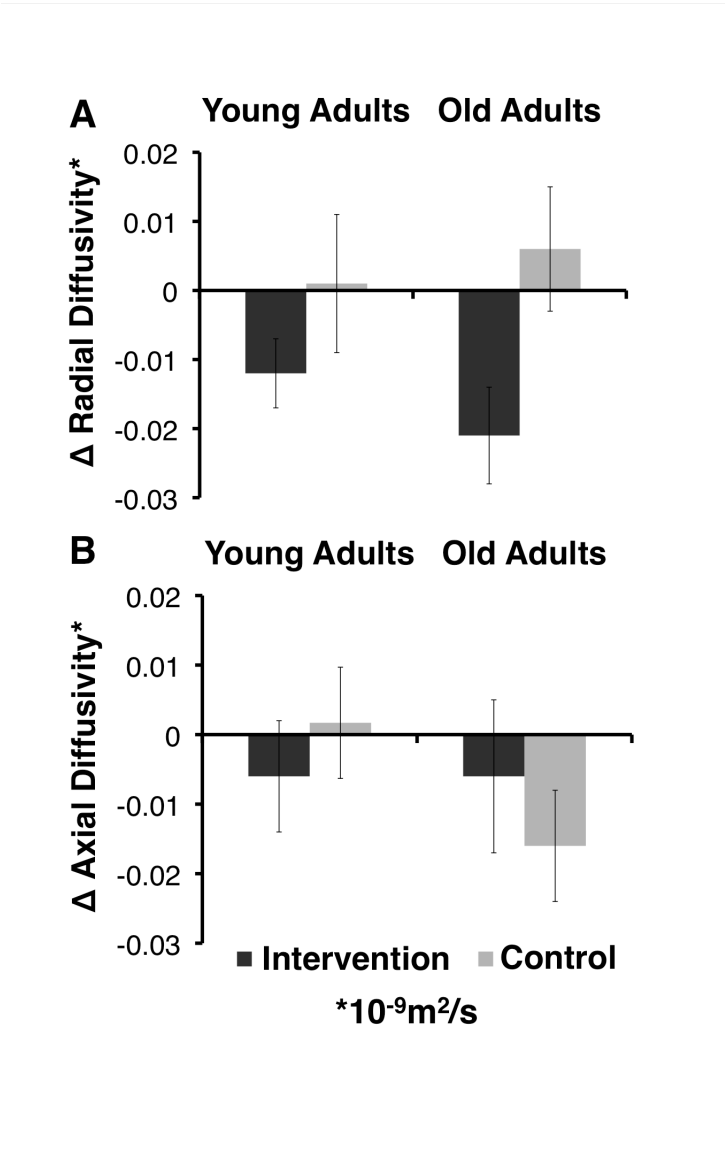


Figure 3.

